

## Mini Review

# Pediatric Malignant Renal Tumors: Current Progress in Treatment

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## Introduction

Malignant renal tumors account for approximately 7% of childhood malignancies, and include a spectrum of pathologies that may challenge the clinician in choosing the optimal treatment [1]. The purpose of this article is to provide a comprehensive overview regarding the spectrum of renal tumors in the pediatric population.

## Wilms Tumor (WT, Nephroblastoma)

Wilms tumor (WT) is the second most common intra-abdominal cancer and accounts for about 95% of all renal tumors in childhood [2]. The incidence of Wilms tumor is 7.1 cases per 1 million children younger than 15 years. About 75% of children are diagnosed between 2 and 5 years of age, and the median age is 3.5 years. Bilateral WT represent 4-7% of all patients [3].

Clinically, WT typically presents as an asymptomatic abdominal mass. Gross hematuria, abdominal pain, or hypertension can be observed in up to a quarter of patients. About 10% of WT have haematogenous spread, most commonly to the lungs (85%), liver (10%) and only very rarely to the bones and brain [4]. WT can be separated into the two prognostic groups on the basis of tumor histopathology: favorable histology (FH) and unfavorable histology (focal anaplasia or diffuse anaplasia) [5]. Anaplastic tumors often express p53 on immunohistochemical staining and bear mutants in the TP53 gene. Diffuse anaplasia and when it identified at advanced stages is associated with poor prognosis [6].

Nephrogenic rests are abnormally retained embryonic kidney precursor cells arranged in clusters. Nephrogenic rests are found in about 35% of kidneys with unilateral Wilms tumor, and nearly 100% of kidneys with bilateral Wilms tumor. The term nephroblastomatosis is defined as the presence of diffuse or multifocal nephrogenic rests. Patients with nephrogenic rest in a kidney removed for nephroblastoma are considered at increased risk for tumor formation in the remaining kidney [7].

Approximately, 5% of WT patients have underlying constitutional mutations at 11p13 (WT1) or epigenetic defects at chromosome 11p15 (WT2).

Germline WT1 mutations are more common in children with Wilms tumor and one of the following syndromes: WAGR syndrome (includes Wilms tumor, aniridia, genitourinary anomaly, and mental retardation) [8], Denys-Drash syndrome (includes genitourinary anomalies such as hypospadias, undescended testis) [9], or Frasier syndrome (characterized by male hermaphroditism, primary amenorrhea, chronic renal failure, and other abnormalities) [10].

WT2-related syndromes include Beckwith-Wiedemann syndrome. This is an overgrowth syndrome characterized by asymmetric growth of one or more parts of the body, large tongue, omphalocele or umbilical hernia at birth, creases or pits in the skin near the ears, kidney abnormalities, and hypoglycemia (in neonates) [11].

Several clinical and biological factors contribute to the risk stratification schema for Wilms [1]. The most important prognostic marker is tumor histology. High-risk histology includes Wilms tumor with anaplasia. The second most important determinant is tumor stage. Other factors that contribute to risk stratification include patient age, tumor weight. Molecular features of the tumor such as 1q gain and loss of heterozygosity (LOH) of 1p and 16q. 1q gain is the most powerful predictor of outcome and is associated with an adverse outcome [12,13].

Surgery, chemotherapy, and, in some patients, radiotherapy comprise the treatment for WT.

There are two different approaches to the initial management of WT in childhood. In North America, patients are treated with upfront surgery prior to administration of chemotherapy, as per the National Wilms' Tumour Study (NWTs)/Children's Oncology Group (COG) protocols. In Europe, most children are treated with pre-operative chemotherapy, according to the Soci te' Internationale d'Oncologie Pe'diatrique Renal Tumour Study Group (SIOP) protocols. The COG staging system is based on the initial pathology (in most cases a primary nephrectomy). The SIOP staging is determined after upfront chemotherapy.

COG established standard treatment for Wilms tumor consisting of initial nephrectomy (when feasible) followed by chemotherapy and, in some patients, radiation therapy [14]. This approach allows for early and accurate histologic diagnosis, collection of biologic materials unaltered by therapy, and staging information, such as the presence of tumor spill or tumor involvement in lymph nodes, before chemotherapy is administered.

SIOP provide preoperative chemotherapy before definitive resection for patients with renal tumors. The preoperative chemotherapy with vincristine and dactinomycin given for 4 weeks for all patients aged more than 6 months at diagnosis with localized nephroblastoma. In stage IV it was suggested to administer

preoperatively three drugs (vincristine, dactinomycin, and doxorubicin) for 6 weeks. Regarding stage V patients, pretreatment was expected to lead to a nephron-sparing surgery on at least one side leaving enough functional renal tissue [15].

In both protocols, postoperative chemotherapy is based on vincristine and dactinomycin for stage I and II with favorable histology, with the exception of children younger than 2 years of age with stage I disease and tumors with favorable histology weighing <550g. Vincristine, dactinomycin, and doxorubicin are used for stage III and IV with favorable histology according to COG protocols. SIOP does not recommend the addition of doxorubicin for stage III favorable (intermediate- or low-risk) tumors. Advanced stages (II, III and IV) of tumor with anaplasia or higher-risk tumors demand therapy intensification by introducing other drugs (i.e. cyclophosphamide, ifosfamide, carboplatin, and etoposide) and radiation therapy. Usually, four drugs are selected for this scenario. Stage V disease (bilateral tumors) requires pre-operative chemotherapy with vincristine, dactinomycin, and eventually doxorubicin for 6 to 12 weeks, followed by nephron-sparing surgery (NSS). Stage III patients or patients with anaplastic histology receive local irradiation according to COG, meanwhile SIOP recommends local radiation therapy for stages II and III with anaplasia Wilms tumor. A major tumor rupture requires whole abdominal radiation therapy [16-18].

Despite a significant and fundamental difference in the approach to these tumors, the NWTSG/COG and SIOP outcomes have been remarkably similar with overall survival (OS) over 90% [19].

### Clear Cell Sarcoma of the Kidney (CCSK)

Clear cell sarcoma of the kidney (CCSK) is the second most common renal tumor in children, accounting for 3% to 5% of all childhood cancers. It commonly appears in children younger than 4 years of age. CCSK is an aggressive tumor with a unique predilection for bone and brain metastasis, but can also spread to the lung and abdomen. Symptoms may include abdominal pain, hypertension, and hematuria. Typical presentation includes a large, unilateral, well circumscribed, sharply demarcated mass that compresses the surrounding normal renal parenchyma and displaces the collecting system [20].

The classic microscopic pattern includes cords of round or spindle shaped cells with clear cytoplasm and ovoid to rounded vesicular nuclei with inconspicuous nucleoli. The cells are surrounded by fibrovascular septa ranging from a thin “chicken-wire” arrangement to broad sheets containing an arborizing capillary vasculature [20]. Cytogenetic abnormalities involving recurring translocations in t(10;17)(q22;p13/p12)53 and deletion of 14q24q31 have been described in CCSK [21]. Younger age and stage IV disease have been identified as adverse prognostic factors for event-free survival (EFS) [22].

Current multimodal treatment consists of radical nephrectomy for resectable tumors followed by intensive chemotherapy and radiotherapy.

In the NWT5-5 (COG-Q9401/NCT00002611) trial, children with stages I to IV clear cell sarcoma of the kidney were treated with

a chemotherapeutic regimen combining vincristine, doxorubicin, cyclophosphamide, and etoposide for 15 months. All patients received radiation therapy to the tumor bed. With this treatment, the 5-year EFS was approximately 79%, and the OS was approximately 89% [23].

SIOP trials include pre-operative treatment with weekly vincristine and dactinomycin for a period of 4 weeks for localized disease, and with vincristine, dactinomycin and epirubicin or doxorubicin for 6 weeks for stage IV patients. Tumor nephrectomy was performed immediately in patients younger than 6 months or older than 18 years of age, or 1 week after the last course of pre-operative chemotherapy in patients between 6 months and 18 years of age. Post-operative treatment recommended for CCSK was a three- or four drug regimen used for high risk nephroblastoma patients. Patients with verifiable metastases after 6 weeks of pre-operative treatment, underwent metastectomy or were irradiated at the site of metastasis. In 191 CCSK patients, five year event-free survival (EFS) and overall survival (OS) were 79% and 86% respectively [22].

### Malignant Rhabdoid Tumor of the Kidney (MRTK)

Malignant rhabdoid tumor of the kidney (MRTK) is a rare, highly aggressive cancer accounting for only 2% of all renal tumors in childhood and is characterized by young age (mean age, 11 months) and advanced stage at presentation. Approximately two-thirds of patients will present with advanced-stage disease. Bilateral cases have been reported [24]. MRTK tend to metastasize to the lungs and the brain. As many as 10% to 15% of patients with MRTK also have central nervous system lesions [25].

The staging system used for MRTK is the same system used for Wilms tumor. Histologically, the most distinctive features of MRTK are rather large cells with large vesicular nuclei, a prominent single nucleolus, and in some cells, the presence of globular eosinophilic cytoplasmic inclusions.

More than 95% of rhabdoid tumors have bi-allelic inactivating mutations of SMARCB1. Up to 35% of patients also have a germline mutation in one allele of SMARCB1, which is an additional adverse prognostic indicator [26]. SMARCA4 mutations have been identified in a smaller subset of patients with the closely related atypical teratoid/rhabdoid tumour of the brain [27].

Patients with MRTK continue to have a poor prognosis. In a review of 142 patients from the National Wilms Tumor Studies (NWT5) (NWT5-1, NWT5-2, NWT5-3, NWT5-4, and NWT5-5 [COG-Q9401/NCT00002611]), age and stage were identified as important prognostic factors: Infants younger than 6 months at diagnosis demonstrated a 4-year OS of 9%, whereas OS in patients aged 2 years and older was 41% (highly significant). Patients with stage I and stage II disease had an OS rate of 42%; higher stage was associated with a 16% OS. All but one patient with a CNS lesion (n = 32) died [25].

In SIOP 93-01/2001 trials, most patients received pre-operative therapy with dactinomycin/vincristine followed by post-operative chemotherapy, consisting of etoposide/carboplatin/ifosfamide/doxorubicin, and radiotherapy but OS rates remained poor (25-30%) [28].

A few case reports have demonstrated effectiveness of regimens containing ifosfamide/carboplatin/etoposide alternating with vincristine/doxorubicin/cyclophosphamide in advanced disease and some centres suggest high-dose therapy with stem cell rescue based on these few patients [29].

In an international prospective study of 100 patients with malignant rhabdoid tumors at extracranial sites that included 17 of the kidney, patients were treated with multimodal therapy, including surgery, radiation therapy, and chemotherapy (vincristine, cyclophosphamide, doxorubicin alternating with cyclophosphamide, carboplatin, and etoposide). The 3-year event-free survival (EFS) was 32.3%, and the 3-year overall survival (OS) was 38.4% [30].

## Renal Cell Carcinoma (RCC)

Renal cell carcinoma (RCC) usually develop in adulthood, only rarely in childhood. RCC accounts for 0.3% of all childhood tumors. The average age of presentation is approximately 10–11 years old [31].

Histologic subtypes of RCC include clear cell renal cell carcinoma (CCRCC), papillary renal cell carcinoma (PRCC), chromophobe renal cell carcinoma (ChRCC), multilocular cystic RCC, tubulocystic RCC and Xp11 translocation RCC (Xp11 TRCC). In children, Xp11 TRCC is the most common subtype of RCC and is characterised by translocations involving the transcription factor E3 gene (TFE3) on chromosome Xp11. Xp11 TRCC comprises 20–40% of pediatric RCCs [32].

RCC may present with hematuria, flank pain, and a palpable mass. Metastases most commonly occur in the lungs (40% to 65%) and bones (10% to 42%); however, the liver (35% to 57%), bladder, brain, or pleura (7% to 15%) may also be involved [33]. Abdominal ultrasound with a subsequent CT scan is used to better define the neoplasm. Although RCC typically reveals a large, heterogeneous, solid mass on CT, Distinguishing between RCC and other renal tumors requires histologic examination. Tumor stage appears to be the most important factor for survival.

The mainstay of treatment remains radical nephrectomy with regional lymphadenectomy [34]. Renal-sparing surgery may be considered for carefully selected patients with low-volume localized disease [35]. RCCs are generally resistant to traditional cytotoxic therapies and are poorly responsive to radiotherapy [34]. Responses to cytotoxic chemotherapy generally have not exceeded 10% for any regimen that has been studied in adequate numbers of patients [35]. The 5-year survival for stage I is 90% or higher, for stages II and III it is 50% to 80% and for stage IV is 9% [34].

Immunotherapy, such as interferon- $\alpha$  and interleukin-2, may have some effect on cancer control. Several targeted agents (for example, sorafenib, sunitinib, bevacizumab, temsirolimus, pazopanib and everolimus) have been approved for use in adults with RCC; however, these have undergone limited testing in pediatric patients [36].

Survival of patients with RCC is affected by stage of disease at presentation and the completeness of resection at radical nephrectomy. OS rates for all patients with RCC range from 64% to 87%. The 5-year survival rates for pediatric RCC are 90% or higher for stage I, higher than 80% for stage II, 70% for stage III, and lower than 15% for stage IV [37].

## Congenital Mesoblastic Nephroma

Congenital mesoblastic nephroma is a low grade fibroblastic sarcoma, comprises about 5% of childhood kidney tumors. It is the most common kidney tumor found in infants younger than 3 months, and 90% of cases appear within the first year of life. Twice as many males as females are diagnosed. More than 15% of the cases are detected prenatally [38]. Prenatal ultrasound may be helpful in diagnosis, as it can lead to polyhydramnios (71% of gestations associated with this tumor) [39]. Postnatal CT typically reveals a large, heterogeneous, solid intrarenal mass with smooth margins that enhances to a lesser degree than the adjacent normal renal parenchyma after intravenous contrast administration [40].

Grossly, mesoblastic nephromas appear as solitary, unilateral masses indistinguishable from nephroblastoma. Microscopically, they consist of spindle mesenchymal cells. Based on histopathologic appearances, congenital mesoblastic nephroma is subtyped into classic (24%), cellular (66%), and mixed (10%) types [41]. The cellular variant carries a specific translocation, t(12;15)(p13;q25), involving the ETV6 and NTRK3 genes, similar to the translocation seen in infantile fibrosarcoma [42].

Complete surgical resection via radical nephrectomy is adequate therapy for most patients and reduces the risk of local recurrence. In stage III patients (incomplete resection and/or histologically positive resection margin), or those with cellular subtype, and aged 3 months or older at diagnosis are at increased risk for local and eventually metastatic recurrence. This select group of patients is recommended to have adjuvant chemotherapy (primarily actinomycin/vincristine and sometimes doxorubicin). Infants younger than 2 months with incompletely resected, stage III disease may not need chemotherapy [41,43,44].

Five year event-free survival (FES) rate is 94%, and the overall survival (OS) rate is 96% when diagnosed within the first 7 months of life [42].

## Conclusion

In conclusion, the survival rate of children with malignant renal tumors has improved dramatically since the inception of the prospective randomized trials conducted by various multi-institutional cooperative groups. Future studies may use genetic markers to stratify high-risk patients beyond the traditional staging system and known histological factors.

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